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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
1644	18

DATE MAILED:

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 4/17/01

☑ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11, 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 1-12, 15, 21, 23-25, 27, 28, 30-36, 38-48, 57-76 is/are pending in the application.
Of the above, claim(s) 41-45, 47, 48, 57-63
☐ Claim(s) _____ is/are withdrawn from consideration.
☑ Claim(s) 1-12, 15, 21, 23-25, 27, 28, 30-36, 38-40, 46, 64-76 is/are allowed.
☐ Claim(s) _____ is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

DETAILED ACTION

1. Applicant's amendment, filed 4/17/01 (Paper No. 16), has been entered.
Claims 13-14, 16-20, 22, 26, 29, 37 and 49-50 have been canceled.
Claims 1, 2, 5, 9-12, 15, 21, 23-25, 27-28, 30-31, 33-34, 36, 38, 40 and 46 have been amended.
Claims 64-76 have been added.

Claims 1-12, 15, 21, 23-25, 27, 28, 30-36, 38-40, 46 and 64-76 are being considered as the elected invention.

Claims 41-45, 47,48, 51-63 have been withdrawn from consideration by the examiner 37 CFR 1.142(b), as being drawn to nonelected invention and/or species

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Office Action will be in response to applicant's arguments, filed 4/17/01 (Paper No. 16).
The rejections of record can be found in the previous Office Action (Paper No. 14).

3. Formal drawings and photographs have been submitted which fail to comply with 37 CAR 1.84.
Please see the form PTO-948 previously sent in Paper No. 14.

4. Claims 1-12, 15, 21, 23-25, 27, 28, 30-36, 38-40, 46 and 64-76: It is apparent that the "3D1" and "H2F", "I2R" antibodies and the "CRL-12524 cell line" are required to practice the claimed invention. As required elements, they must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If they are not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the appropriate cell lines/hybridomas which produces these antibodies. See 37 CFP 1.801-1.809.

Applicant's arguments, filed 4/17/01 (Paper No. 16). have been fully considered, but are not found convincing essentially for the reasons of record.

Applicant argues that the prior art antibodies are known and available to the public; given that CRL-12524 cell line was deposited with the ATCC; that the 3D1 is available from the ATCC, as indicated in U.S. Patent No. 6,084,067 and H2F and I2R antibodies were disclosed in Manheimer-Lory (J. Exp. Med. 174: 1639-1652, 1991)

However, biological materials must be known and readily available to the public (See MPEP 2404.01). Neither concept alone is sufficient. The fact that applicant and other members of the public were able to obtain the materials in question from a given depository prior to and after the filing date of the application does not establish the upon issuance of a patent on the application that such material would continue to be accessible to the public. The applicant did not make of record any of the facts and circumstances surrounding the access to the biological materials from the depository, nor is there any evidence as to the depository's policy regarding the material if a patent would be granted. Further, there is no assurance that the depository would allow unlimited access to the material if the application has matured into a patent. In the absence of evidence that the "3D1", "H2F" and "I2R" antibodies / hybridomas are readily available to the public and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, applicant's arguments are not persuasive and the rejection is maintained.

It is noted that the mere reference to a deposit or the biological material itself in any document or publication does not necessarily mean that the deposited biological material is readily available. Even a deposit made under the Budapest Treaty and referenced in a United States or foreign patent document would not necessarily meet the test for known and readily available unless the deposit was made under conditions that are consistent with those specified in these rules, including the provision that requires, with one possible exception, that all restrictions on the accessibility be irrevocably removed by the applicant upon the granting of the patent. Ex parte Hildebrand , 15 USPQ2d 1662 (Bd Pat. App. & Int. 1990). See MPEP 2404.01

With respect to applicant's comments that these materials are obtainable by a repeatable methods set forth in the specification; given the high polymorphism of antibodies; the skilled artisan could not predict the sequence of the claims specific 3D1, H2F and I2R antbodies by simply relying upon the disclosed methods steps. Therefore, applicant's arguments are not persuasive and the rejection is maintained.

As pointed out previously, in addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

Again, as pointed out previously, it has been noted that if the claimed and disclosed amino acid sequences or nucleic acid sequences set forth in the instant application encode the entire "3D1", "H2F" and "I2R" antibodies; then a deposit for said "antibodies (cell lines/hybridomas) are not required. The sequence of an entire immunoglobulin satisfies the biological deposit of said immunoglobulin.

5. Claims 1-12, 15, 21, 23-25, 27, 28, 30-36, 38-40, 46 and 64-76 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-12, 15, 21, 23-25, 27, 28, 30-36, 38-40, 46 and 64-76 are indefinite in the recitation of "3D1" and "H2F", "I2R" antibodies because their characteristics are not known. The use of "3D1" and "H2F", "I2R" antibodies" as the sole means of identifying the claimed antibodies renders the claims indefinite because these "names" are merely laboratory designations which do not clearly define the claimed products; since different laboratories may use the same laboratory designations to define completely distinct cell lines or hybridomas.

As pointed out above; the disclosure of the sequence for an entire immunoglobulin satisfies the biological deposit of said immunoglobulin and amending the claims to incorporate the appropriate SEQ ID NOS. would render the claims definite.

Applicant's arguments have been fully considered, but are not found convincing essentially for the reasons of record.

Applicant's reliance upon the 3D1, H2F and I2R disclosed in the specification and in U.S. Patent No. 6,084,067 and Manheimer-Lory et al. (J. Exp. Med. 174: 1639-1652, 1991) antibody is acknowledged.

As pointed out in the last Office Action, the use of "3D1" and "H2F", "I2R" antibodies" as the sole means of identifying the claimed antibodies renders the claims indefinite because these "names" are merely laboratory designations which do not clearly define the claimed products; since different laboratories may use the same laboratory designations to define completely distinct cell lines or hybridomas. There are many subjective and objective characteristics that can be associated with an antibody, including the 3D1" and "H2F", "I2R" antibodies. In addition, a particular biological cell line such as a hybridoma can undergo changes resulting in microheterogeneity in the products such as antibodies that such cell lines can reproduce. To obviate any ambiguity as to whether the designations 3D1" and "H2F", "I2R" antibodies refers to a particular characteristic (e.g. B7-2-specificity) , to a particular set of characteristics (e.g. structural and/or functional) or to a particular cell line (e.g. ATCC HB 11686) and all of its corresponding characteristics; the recitation of the deposit cell line is required. The 3D1" and "H2F", "I2R" designations are an incomplete and ambiguous description of the biological materials in the absence of the appropriate deposit accession numbers . It is not clear why applicant does not want to recite the appropriate ATCC accession number in conjunction with 3D1" and "H2F", "I2R" antibodies, unless these "designations" are intended to mean something other than the particular antibodies produced by the particular deposited hybridomas. Applicant's arguments are not found persuasive and the rejection is maintained.

B) Claims 24, 28 are indefinite in the recitation of " stringent conditions" because the metes and bounds of such conditions are ambiguous and unclear and, in turn, the metes and bounds of the claimed "nucleic acids" are not defined.

Applicant's arguments, filed 4/17/01 (Paper No. 16), have been fully considered, but are not found convincing essentially for the reasons of record.

Applicant submits that "stringent hybridization conditions" was an art recognized term at the time the invention was made and therefore one of skill in the art would have known what applicant regarded as the invention with respect to this term.

In contrast to applicant's assertions; the metes and bounds of "stringent hybridization conditions" are not clearly defined. The term in clam is a relative term which renders the claim indefinite. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Again, applicant is invited to point out a definition for "stringent conditions" in the specification as filed; if one is available rather than relying upon asserted definitions.

Alternatively, applicant has been invited to consider amending the claims to recite functional language as well.

C) The applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06

6. Applicant's amended claims, filed 4/17/01 (Paper No. 16), have obviated the previous rejection under 35 U.S.C. § 102(e) as being anticipated by Freeman et al.. (U.S. Patent No. 6,084,067) as it applies to the instant claims.

7. Claims 1-12, 15, 21, 23-25, 27, 28, 30-36, 38-40, 46 and 64-76 are rejected under 35 U.S.C. § 103 as being unpatentable over Freeman et al.. (U.S. Patent No. 6,084,067) in view of art known gene cloning and expression strategies for deriving recombinant antibodies and fragments thereof, as disclosed/admitted on pages 10-29 or Examples I (only indicated as Exemplification on page 35 of the specification/ II/III of the instant specification or as cited by references on the 1449. It would have been have been a matter of routine experimentation well within the ordinary skill level of art to generate chimeric, humanized or recombinant HF2.3D1-/B7-2-specific antibodies, nucleic acids encoding said antibodies, vectors, host cells, methods of making and compositions thereof; given the HF2.3D1 antibody and hybridoma and its associated properties known in the prior art. The instant claims are drawn to HF2.3D1-/B7-2-specific antibodies and fragments thereof and nucleic acids encoding said antibodies, particularly the 3D1/B7-2 specificity.

Applicant's arguments, filed 4/17/01 (Paper No. 16), have been fully considered, but are not found convincing essentially for the reasons of record set forth in Paper No. 14.

Applicant argues that the claims are drawn to humanized immunoglobulins which bind B7-2, wherein the antigen binding domains are derived from 3D1 and the framework domains/residues are derived form the H2F and I2R antibodies.

Applicant relies upon the lack of disclosure by the prior art of the specific sequences set forth in the claims, including the derivation of framework regions of the H2F and I2R antibodies.

Applicant asserts that the prior art does not disclose that the CRL 12524 cell line was deposited with the ATCC.

Applicant traverse the reliance upon modifying the referenced 3D1 antibody by designing known parameters, techniques and computer programs (ABMOD and ENCODE) at the time the invention was made.

Applicant argues that the prior art lacks proper suggestion or motivation as well as a reasonable expectation of success of the claimed invention at the time the invention was made.

Applicant argues that claimed invention would not be obvious given the choices among all of the possible human antibodies in deriving humanized 3D1 antibodies and nucleic acids encoding said antibodies.

Applicant asserts that the inventors found that the I2R and H2F antibodies had high homology to the B7-2-specific 3D1 antibody in deriving humanized B7-2-specific antibodies based upon the 3D1 specificity.

In contrast to applicant's assertions, it appears that applicant has relied upon the selection of the I2R and H2F framework modifications of the B7-2-specific humanized antibodies based upon the B7-2-specific 3D1 antibody, as disclosed in Example 2 of the instant specification.

For example, page 37, paragraph 1 discloses that the "The computer programs ABMOD and ENCODE (Levitt et al. J. Mol. Biol. 168: 595 (1983)) were used to construct a molecular model of the 3D1 variable domain which was used to locate the amino acids in the 3D1 framework that are close enough to the CDRs to potentially interact with them. To design the humanized 3D1 heavy and light chain variable regions, the CDRs from the mouse 3D1 heavy chain were grafted into the framework regions of the human I2R heavy chain and the CDRs from the mouse 3D1 light chain grafted into the framework regions of the human H2F light chain. At framework positions where the computer model suggested significant contact with the CDRs, the amino acids from the mouse antibody were substituted for the original human framework residues."

The following of record is noted herein.

It appears that the instant "3D1" is the same as the "HF2.3D1" B7-2-specific antibody of the prior art.

This reference differs from the instant invention by not disclosing the particular amino acid or nucleic acids of the HF2.3D1/ 3D1 antibody , nor of the particular "H2F", "I2R" antibodies and the "CRL-12524 cell line per se.

However, as clearly taught by Freeman et al.;, it was obvious to one of ordinary skill in the art at the time the invention was made to humanize various antibodies, including "HF2.3D1" B7-2-specific antibody, particularly in view of its specificity and functional properties known at the time the invention was made.

Given the availability of the HF2.3D1/ 3D1 antibody and hybridoma together to others with general immunoglobulin gene cloning and expression strategies, it would have been have been a matter of routine experimentation well within the ordinary skill level of art to generate chimeric or humanized HF2.3D1/ 3D1 antibody B7-2-specific antibodies, nucleic acids encoding said antibodies, vectors, host cells, methods of making and compositions thereof. Given the highly conserved nature of immunoglobulin gene organization and structure and the availability of probes and PCR primers for immunoglobulin gene cloning, one of ordinary skill in the art could have isolated the functionally rearranged heavy and light chain variable regions from the HF2.3D1 hybridoma cell line and determined their sequences with a complete expectation of success. For example, the ordinary artisan does not need to determine the amino acid sequences of a rearranged V (variable) region before cloning. The claims do not differ unexpectedly or unobviously from what one of ordinary skill in the art would have expected to obtain given the known HF2.3D1 hybridoma thereof, the known heavy and light chain and the art known techniques regarding the production of chimeric antibodies, as acknowledged by the number of available art known procedures disclosed in the instant specification and cited on the Information Disclosure Statement. The claimed DNA sequences must encode a recombinant antibody comprising heavy and/or light chain variable regions of the instant B7-2-specific antibodies.

It is noted Examples 1/II/III of the specification discloses that the design of the instant "3D1", "H2F", "I2R" antibodies and the "CRL-12524 cell line were humanized versions (and associated nucleic acids, vectors, hosts cells) of the "3D1"/B7-2-specific antibody. Furthermore, it is acknowledged that the modifications of "3D1" antibody were designed on known parameters, techniques and computer programs (ABMOD and ENCODE) at the time the invention was made (also see 1449 references), including modifications to the framework regions to allow the recombinant antibodies to maintain substantial affinity to B7-2. Therefore, the claims limitations were expected functional products and modifications of making and preparing humanized HF2.3D1 /B7-2-specific antibodies at the time the invention was made.

Immunoglobulin gene structure and organization were well understood in the art a the time the claimed invention was made and that strategies for cloning the DNAs encoding immunoglobulin variable regions genes were well established in the art at the time the claimed invention was made, as were methods for the production of DNA constructs encoding immunoglobulin variable regions. In addition, it was known at the time the invention was made that the benefits of producing recombinant antibodies to reduce the immunogenicity of therapeutic and diagnostic antibodies in human patients. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references and admitted prior art, especially in the absence of evidence to the contrary.

8. No claim is allowed.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Phillip Gambel, Ph.D.
Primary Examiner
Technology Center 1600
June 25, 2001